PTO/SB/68 (04-01)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

In re Application of	
Application Number: 08/509,359	Filed: 07-31-95
Art Unit	Examiner

RECEIVED
JUL 30 2002
File Information Unit

Paper No. #44

Assistant Commissioner for Patents
Washington, DC 20231

1. ☑ I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

☐ (A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____,

United States Patent Number 5,986,054, column _____, line _____, or

an International Application which was filed on or after November 29, 2000 and which designates the United States, WIPO Pub. No. _____, page _____, line _____.

☐ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or 1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. ☑ I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Rahel Haile
Signature

7-30-02
Date

Rahel Haile
Typed or printed name

FOR PTO USE ONLY	
Approved by: _____ (Initials)	
Unit: _____	

US005986054A

United States Patent [19]

St. George-Hyslop et al.

[11] Patent Number: 5,986,054

[45] Date of Patent: Nov. 16, 1999

[54] GENETIC SEQUENCES AND PROTEINS RELATED TO ALZHEIMER'S DISEASE

[75] Inventors: **Peter H. St. George-Hyslop; Johanna M. Rommens; Paul E. Fraser**, all of Toronto, Canada

[73] Assignees: **The Hospital for Sick Children, HSC Research and Development Limited Partnership; The Governing Council of the University of Toronto**, both of Canada

[21] Appl. No.: **08/592,541**

[22] Filed: **Jan. 26, 1996**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/509,359, Jul. 31, 1995, which is a continuation-in-part of application No. 08/496,841, Jun. 28, 1995, which is a continuation-in-part of application No. 08/431,048, Apr. 28, 1995.

[51] **Int. Cl.**[6] **C07K 14/00**; C12P 21/06

[52] **U.S. Cl.** **530/350**; 435/69.1

[58] **Field of Search** 530/350; 435/69.1

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,262,332	11/1993	Selkoe	436/518
5,297,562	3/1994	Potter	128/898

FOREIGN PATENT DOCUMENTS

2054302	4/1992	Canada .
2071105	12/1992	Canada .
2096911	11/1993	Canada .
91/19810	12/1991	WIPO .
94/00569	1/1994	WIPO .
94/10569	5/1994	WIPO .
94/23049	10/1994	WIPO .
WO 97/03086	1/1997	WIPO .
WO 97/03192	1/1997	WIPO .
WO 97/03999	2/1997	WIPO .

OTHER PUBLICATIONS

Barinaga, Marcia, "New Alzheimer's Gene Found," *Science*, vol. 268:1845–1846 (1995).

Barinago, Marcia, "Missing Alzheimer's Gene Found," *Science* vol. 269:81–92 (1995).

Campion, et al., "Mutations of the presenilin I gene in families with early-onset Alzheimer's disease," *Human Molecular Genetics*, vol. 4, No. 12:2373–2377 (1995).

Chartier-Harlin, et al., "Early onset Alzheimer's disease caused by mutations at codon 717 of the β–amyloid precursor protein gene," *Nature*, vol. 353:844–846 (1991).

Cruts, et al., "Molecular genetic analysis of familial early-onset Alzheimer's disease linked to chromosome 14q24.3," *Human Molecular Genetics*, vol. 4, No. 12:2363–2371 (1995).

Foncin, et al., "Alzheimer's Presenile dementia transmitted in an exteneded kindred," *Rev. Neurol (Paris)*, vol. 141:194–202 (1985).

Goate, et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," *Nature*, vol. 349:704–706 (1991).

Goudsmit, et al., "Familial Alzheimer's Disease in two kindreds of the same geographic and ethnic origin: a clinical and genetic study," *J. Neurol. Sci.*, vol. 49:79–89 (1981).

Gyapay, et al., "The 1993–94 Genethon human genetic linkage map," *Nature Genetics*, vol. 7:246–311 (1994).

Karlinsky, et al., "Molecular and prospective phenotypic characterization of a pedigree with familial Alzheimer's disease and a missense mutation in codon 717 of the β–amyloid precursor protein (APP) gene," *Neurology*, vol. 42:1445–1453 (1992).

Katzman, R., "Alzheimer's Disease," *N.Eng.J.Med.*, vol. 314:964–973, (1986).

Levy-Lahad, et al., "A Familiar Alzheimer's Disease Locus on Chromosome I," *Science*, vol. 269:970–973 (1995).

Levy-Lahad, et al., "Candidate Gene for the Chromsome I Familial Alzheimer's Disease Locus," *Science*, vol. 269:973–977 (1995).

Mullan, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N–terminus of β–amyloid," *Nature Genetics*, vol. 1:345–347 (1992).

Mullan, et al., "A locus for familial early–onset Alzheimer's disease on the long arm of chromosome 14, proximal to the α1–antichymotrypsin gene," *Nature Genetics*, vol. 2:340–342 (1992).

Murrell, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's Disease," *Science*, vol. 254:97–99 (1991).

Nee, et al., "A family with histolgically confirmed Alzheimer's Disease," *Arch. Neurol*, vol. 40:203–208 (1983).

Pericak-Vance, et al., "Genetic linkage studies in Alzheimer's Disease families," *Exp. Neurol*, vol. 102:271–279 (1988).

Rogaev, et al., "Analysis of the c–FOS gene on chromosome 14 and the promoter of the amyloid precursor protein gene in familial Alzheimer's disease," *Neurology*, vol. 43:2275–2279 (1993).

Rogeav, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome I related to the Alzheimer's disease type 3 gene," *Nature*, vol. 376:775–778 (1995).

Rommens, et al., "A transcription map of the region containing the Huntington disease gene," *Hum. Molec. Genet.*, vol. 2:901–907 (1993).

Sherrington, et al., "Cloning of a gene bearing missence mutations in early–onset familial Alzheimer's disease," *Nature*, vol. 375:754–760 (1995).

(List continued on next page.)

Primary Examiner—Karen Carlson

Attorney, Agent, or Firm—Lerner, David, Littenberg, Krumholz & Mentlik

[57] **ABSTRACT**

The present invention describes the identification, isolation and cloning of two human presenilin genes, PS-1 and PS-2, mutations in which lead to Familial Alzheimer's Disease. Also identified are presenilin homologue genes in mice, *C. elegans* and *D. melanogaster*. Transcripts and products of these genes are useful in detecting and diagnosing Alzheimer's disease, developing therapeutics for treatment of Alzheimer's disease, as well as the isolation and manufacture of the protein and the constructions of transgenic animals expressing the mutant genes.

29 Claims, 12 Drawing Sheets

OTHER PUBLICATIONS

St. George–Hyslop, et al., "Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder," *Nature*, vol. 347:194–197 (1990).

St. George–Hyslop, et al., "Genetic evidence for a novel familial Alzheimer's disease locus on chromosome 14," *Nature Genetics*, vol:2:330–334 (1992).

St. George–Hyslop, et al., "Alzheimers Disease and Possible Gene Interaction," *Science*, vol. 263:537 (1994).

Saunders, et al., "Association of apolipoprotein E allele e4 with the late–onset familial and sporadic Alzheimer's disease," *Neurology*, vol. 43:1467–1472 (1993).

Schellenberg, et al., "Genetic Linkage Evidence for a Familial Alzheimer's Disease Locus on Chromosome 14," *Science*, vol. 258:668–670 (1992).

Schellenberg, et al., "Chromosome 14 and Late–Onset Familial Alzheimer Disease (FAD)," *Am. J. Hum. Genet.*, vol. 53:619–628 (1993).

Strittmatter, et al., "Apolipoprotein E: hgh avidity binding to β–amyloid and increased frequency of type 4 allele in late–onset familial Alzheimer's disease," *Proc. Nat'l. Acad. Sci. USA*, vol. 90:1977–1981 (1993).

Van Broeckhoven, et al., "Mapping of a gene predisposing to early–onset Alzheimer's disease to chromosome 14q24.3," *Nature Genetics*, vol. 2:335–339 (1992).

Van Broeckhoven, Christine, "Presenilins and Alzheimer disease," *Nature Genetics*, vol. 11:230–232 (1995).

Wong, et al., "Mutation of the gene for the human lysosomal serine protease Cathepsin G is not the cause of aberrant APP processing in familial Alzheimer disease," *Neurosci. Lett*, vol. 152:96–98 (1993).

Fleischhauer, K., et al., EMBL Sequence Data Library, Mar. 31, 1992, Accession No. X63522.

YU, V.C., et al., EMBL Sequence Data Library, Dec. 10, 1991, Accession No. M81766.

Sevigny, G., et al., EMBL Sequence Data Library, Jan. 7, 1995, Accession No. U17104.

Johansson, E., et al., The Journal of Biological Chemistry, 270(35):20615–20620 (1995).

Pawlak, A., et al., EMBL Sequence Data Library, Dec. 20, 1994,Accession No. T18858.

Auffray, C., et al., EMBL Sequence Data Library, Feb. 17, 1995, Accession No. F08730.

Walkley, N.A., et al., EMBL Sequence Data Library, Jan. 1, 1994, Accession No. X74801.

Hillier, L., et al., EMBL Sequence Data Library, Apr. 22, 1995, Accession No. R12984.

Fujiwara, T., et al., EMBL Sequence Data Library, Aug. 25, 1995, Accession No. D55326.

Hillier, L., et al., EMBL Sequence Data Library, Mar. 6, 1995, Accession No. T64843.

Zahraoui, A., et al., EMBL Sequence Data Library, Jul. 22, 1994, Accession No. X56740.

Drivas, G.T., et al., EMBL Sequence Data Library, Feb. 19, 1991, Accession No. X53143.

Chambon, P., et al., EMBL Sequence Data Library, Feb. 7, 1992, Accession No. M84820.